Advances in Prostate Cancer Treatment

Highlights from the 2nd International Prostate Cancer Congress, St. Thomas, U.S. Virgin Islands, July 17–20, 2002

[*Rev Urol.* 2003;5(2):111–117]

Key words: Prostate-specific antigen • Hormone-refractory prostate cancer • Radiotherapy • Androgen blockade • Radioimmunoscintigraphy • Nomograms

The 2nd International Prostate Cancer Congress was held July 17-20, 2002 in St. Thomas at the Marriott Frenchman's Reef Resort. The conference was moderated by co-chairmen Drs. Oliver Sartor and David McLeod and included a faculty composed of world-leading experts in medical, radiation, and urologic oncology. The meeting provided a comprehensive update on the biology, screening, diagnosis, and management of prostate cancer and was attended by medical oncologists, urologists, and radiation oncologists.

Reviewed by Matthew B. Gretzer, MD and Alan W. Partin, MD, PhD, The James Buchanan Brady Urological Institute, Johns Hopkins Hospital, Baltimore, MD.

State of the Art

The opening session introduced state-of-the-art advances in the field of prostate cancer. Dr. Alan Partin discussed the impact of free and complexed prostate-specific antigen (PSA) in cancer screening, focusing on recent developments regarding the various forms of free (uncomplexed) PSA in serum.[1] One of these isoforms, pPSA, a precursor form of PSA in serum, has been associated with cancer and may provide additional specificity for cancer detection in the free PSA "gray zone" from 10%–25%.[1-3] Furthermore, the discovery of various additional isoforms of pPSA may offer insight into stage and grade. Another form of free PSA, labeled BPSA, has been associated with prostate benign prostatic hyperplasia (BPH) transition zone tissue.[2] As a potential marker for BPH, BPSA serum levels may be used to follow the effectiveness of BPH therapies such as 5-α-reductase inhibitors.[1,4] Although previous studies evaluating BPSA have failed to discriminate prostate cancer from BPH, new immunoassays combining BPSA and

pPSA may provide a powerful new tool for the study of prostate disease.

Dr. Daniel Petrylak presented an update on treatment options for men with hormone-refractory prostate cancer. Whereas therapy employing mitoxantrone and corticosteroids has been shown to provide palliation from bone pain, improvements in survival have yet to be observed.[5,6] Recent studies evaluating estramustine and taxane-based regimens demonstrate promise in the treatment of hormone-refractory disease. Early clinical trials have shown that taxanes, either as single agents or combined with estramustine, exhibit significant activity in terms of response rate, decline in PSA level, and reduction in bone pain for men with hormone-refractory disease.[7-10] Side effects related to estramustine therapy have included cerebral vascular accident and deep venous thrombosis. Strategies to reduce these complications have included prophylactic administration of warfarin and dose adjustment. Early trials with estramustine and taxane appear promising, but the results of ongoing Phase III trials are awaited and should aid in determining whether the apparent improvements from these early trials are a result of stage migration since the introduction of PSA screening.

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Dr. Carlos Perez presented an update of the technical principles and results comparing 3-dimensional conformal radiotherapy (3D CRT) with standard radiotherapy (SRT) for the treatment of localized prostate cancer (T1c/T2).[11] In a retrospective study, 312 men underwent 3D CRT and 135 received SRT.[11] Citing similar results from other comparative studies,[12-13] Perez observed higher 5-year chemical disease-free survival with CRT than with SRT (75% vs 65%). Furthermore, dose-escalation studies among men treated with CRT illustrated fewer pelvic failures with doses greater than 72 Gy.[14,15] Higher doses were found to benefit men with pre-radiation PSAs of 10 ng/mL or above and Gleason sums above 4. Toxicities with CRT and even within the dose-escalation studies were significantly lower than with SRT.[16-18] Technical advances have enhanced the ability of conformal radiation portals to target precise volume and reduce the irradiation of adjacent normal tissues.[16]

An overview of prostate cancer pathology was presented by Dr. David Bostwick. He stressed the importance of architectural and cytologic findings for definitive diagnosis of malignancy and included examples of the irregular and haphazard arrangement of malignant acini, the variable presence of basal cells in normal versus malignant glands, and the nucleolar abnormalities observed within cancerous cells.[19] Dr. Bostwick also commented on two pathologic indications for repeat biopsy: high-grade prostatic intraepithelial neoplasia, and atypical acinar proliferation suspicious for but not diagnostic of malignancy (ASAP).[20,21] These two diagnoses remain a vexing gray zone for many urologists for which a uniform management algorithm has yet to be determined. Although ASAP represents a controversial histologic diagnosis, Dr. Bostwick supports this histologic finding as a valid diagnostic category worthy of continued vigilance, the extent of which to be tempered by the clinician and patient.

Strategies to reduce these complications have included prophylactic administration of warfarin.

Cooperative Trials and Promising New Therapies

A cooperative group update for the Radiation Therapy Oncology Group (RTOG), Southwest Oncology Group (SWOG), and Eastern Cooperative Oncology Group (ECOG) highlighted the current status of ongoing prostate cancer trials. Dr. Mack Roach presented an overview and rationale for the ongoing RTOG trials. Current RTOG trials are addressing questions concerning radiation dose and type (3D RTOG 01-26 & BT), the role of adjuvant chemotherapy (RTOG 9902), optimal duration of neoadjuvant hormonal therapy (RTOG 9910), and postoperative management (RTOG 9601 and 0011).

Dr. David Crawford reviewed findings from many of the SWOG trials that evaluate the efficacy of combined androgen blockade with nonsteroidal antiandrogens for advanced prostate cancer. Of 20 different trials (n = 6320), the odds ratio of pooled results exhibited a 5% improvement in the percentage of men surviving at 5 years with combined androgen blockade with nonsteroidal antiandrogens as well as improvements in progression-free survival at 1 year.[22]

Dr. George Wilding outlined the menu of clinical trials currently active in ECOG. The vast array of trials encompass adjuvant therapy in early PSA failures following primary therapy, hormone-naïve and hormone-

refractory prostate cancer, palliation, and genetics.

A review of the recent literature on promising new molecular-based therapeutic strategies was presented by Dr. Kevin Kelly.[23] Advances in the understanding of the molecular biology of prostate cancer have resulted in the development of innovative gene and immunotherapies. Novel gene therapies include replacement therapies aimed at correcting defective genes and cytoreductive strategies that, together with gene replacement, rely on generating local or systemic anticancer effects using vectors designed to kill prostate cancer cells using immunological or cytotoxic mechanisms.[24,25] Identified as the immune system's professional antigen-presenting cells, dendritic cells offer a mode of directing an immune response against specific antigens located on prostate cancer cells.[26] Other promising therapies include the use of compounds to induce apoptosis, such as exisulind, the sulfone metabolite of sulindac, which has shown potent proapoptotic properties in early trials.[27] Histone deacetylases also appear to aid in cancer therapy by inducing cellular arrest and apoptosis; they are currently being introduced into early clinical trials.[28]

Novel gene therapies include replacement therapies aimed at correcting defective genes.

Prevention

Drs. Ian Thompson and Mark Klein provided the attendees with informative sessions regarding prevention trials currently under way. The Prostate Cancer Prevention Trial (PCPT) randomizing 18,000 men with normal digital rectal exam and PSA below 3 ng/mL to finasteride or placebo will help determine the efficacy of finasteride in reducing the period-specific period prevalence of prostate cancer.[29] This trial, which opened in 1993, is now closing, and men in this study are currently undergoing prostate biopsy following 7 years of treatment. The results of this study are expected to be released by 2004 or 2005.

Prompted by the provocative secondary National Cancer Institute (NCI) Phase III data on selenium and vitamin E and prostate cancer incidence, the Selenium and Vitamin E Cancer Prevention Trial (SELECT) is currently recruiting men to assess the effects of selenium and vitamin E alone and in combination on the clinical incidence of prostate cancer.[30,31] This double-blind placebo-controlled study aims to enroll 32,400 healthy men of 50 (African American) or 55 (all other races) years of age. Following a recruitment period of 5 years, the effects of these nutrients at reducing prostate cancer will be evaluated over 7 to 12 years. The antioxidant effects of certain dietary components such as isoflavones and lycopenes on prostate cancer risk and progression were also discussed during this session.[32,33] Ongoing trials are examining the role of soy-based dietary supplementation as therapy for men with various clinical presentations of prostate cancer.[34,35] The antioxidant effect of lycopenes has also been the focus of many clinical studies. To date, many of these clinical investigations reveal promising beneficial evidence supporting an antioxidant effect of lycopenes.[36-38]

Dr. Michael Manyak presented current and promising new techniques used for imaging prostate cancer. Controversy regarding the ProstaScint scan garnered much discussion among the participants, as was evidenced by the variability of its use among the attendees. Results from Phase III trials were presented,[39-41] and although the positive predictive value has been shown to be modest at best, Dr. Manyak stressed that the strong negative predictive value of this study should not be overshadowed.[42] Promising early results were presented with new imaging agents for application in radioimmunoscintigraphy. Also presented was the potential of optical coherence tomography.[43] This novel imaging modality employs light and is similar to ultrasound in providing real-time 2-dimensional images. Advantages include thin cuts in the 2–3 mm range, imaging through air or water, imaging soft tissue or bone, and very high structural resolution. Currently being investigated in other clinical fields, this modality holds promise in urologic applications.

Hormonal Therapy

Despite limited established clinical evidence to support widespread application, increasing use of primary and neoadjuvant androgen-deprivation therapy continues to be observed. Dr. Peter Carrol presented an update of current data from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database, which records treatment decisions of men diagnosed with prostate cancer treated with radical prostatectomy (RP), radiation therapy (RT), or hormonal therapy (HT).[44] Following risk stratification of these men into low, intermediate, or high, this database reveals that the use of primary androgen therapy is increasing in all risk groups, with the greatest use among men in the low-risk group. The use of hormonal neoadjuvant therapy is also increasing among

men treated with RP and to a larger extent among men treated with RT.

Dr. McLeod presented an update of the early prostate cancer program evaluating bicalutamide versus placebo in men with prostate cancer treated with RP, RT, or watchful waiting.[45] This program consists of 3 identically designed trials at different locations around the world. Overall time to progression at 5 years reveals 5% less progression in men receiving androgen-deprivation therapy.

To evaluate further the benefit of neoadjuvant therapy with RT, Dr. Roach discussed the different RTOG trials evaluating this important question. An example of one such study, RTOG 8610, evaluated whether 4 months of HT with RT showed improvement over RT alone for men with T3 disease.[46] Survival advantages have been illustrated for these men, as evidenced by reduction in PSA recurrence and improved local control.

Dr. Crawford presented an overview of studies evaluating the role of early versus late HT in men with locally advanced disease and positive lymph node disease.[47] In these trials an apparent survival advantage was observed when therapy was administered early. Furthermore, the advantage was more pronounced in men with lesser tumor burdens. Dr. Crawford surmised from these results that men with rising PSAs after failed local therapy may benefit from this therapeutic intervention.

Dr. Sartor presented an overview of HT focusing on new therapeutic agents, new delivery systems, and utilization of traditional agents using novel approaches. Some of these include newer formulations of luteinizing hormone-releasing hormone (LHRH) agonists, LHRH antagonists, 5-α-reductase inhibitors, and estrogen receptor alpha antagonists.[48-50]

Risk Stratification

Several speakers presented updates regarding the application of presurgical variables and nomograms in an effort to improve predictive staging and therapeutic decision-making. Dr. Partin discussed a rational approach to selecting appropriate patients for surgery. As more men are presenting with T1c, Dr. Partin presented an updated version of the "Partin tables" that more accurately reflects recent trends on presentation and pathologic stage.[51]

Eventual risk groups that will predict prostate cancer–specific mortality will include not only tumor burden and biological aggressiveness, but also information regarding the patient's overall health and life expectancy and the treatment utilized.

In addition, recent work was discussed in substratifying men with T1c into low and high risk of biochemical recurrence using PSA, Gleason sum, and quantitative histologic pathology of biopsy material.[52] Dr. Anthony D'Amico reviewed his work regarding combined-modality staging of men with prostate cancer into low, intermediate, and high risk to predict PSA failure.[53] Dr. D'Amico stressed that although risk groups that are defined using any stratification modality are adequate for predicting PSA outcome for the vast majority of patients with clinically localized prostate cancer, it is too soon to tell if they will succeed in predicting prostate cancer mortality. Eventual risk groups that will predict prostate cancer–specific mortality will include not only tumor burden and biological aggressiveness, but also information regarding the patient's overall health and life expectancy and the treatment utilized.

Dr. Michael Kattan reviewed the concepts of risk stratification and the development and use of nomograms as predictive tools.[54,55] Whereas the use and application of predictive nomograms aid in patient selection and decision-making, current nomograms are based on the use of PSA as a surrogate end point. Dr. Kattan stressed that until newer nomograms are developed that include information regarding the probability of developing metastasis and death from cancer, use of current nomograms should only be as an aid and should not replace the decision-making process utilized by the treating clinician.[54,55]

Several speakers also addressed whether patients identified by these staging modalities and nomograms as being at high risk for PSA failure following definitive therapy may benefit from early adjuvant therapy. Dr. Mitchell Anscher discussed adjuvant RT following radical prostatectomy before rising PSA.[56,57] Citing available retrospective data,[58-60] Dr. Anscher supports the use of adjuvant RT following radical prostatectomy for men at high risk for local recurrence rather than delaying treatment until PSA begins to rise. Dr. William Oh presented data regarding new approaches to patients at high relapse risk following local therapy. In a recent Phase II study, patients with high-risk localized prostate cancer (T3) were treated with weekly docetaxel prior to radical prostatectomy.[61] Although final pathologic results are pending, preliminary data illustrated lack of complete pathologic response. Together with other trials,[62-64] these reports illustrate the feasibility of neoadjuvant cytotoxic chemotherapy; however, lack of complete pathologic response is discouraging.

Prostate Cancer and the Bone

Dr. Leland Chung reviewed theories explaining the pathogenesis of bone metastasis in prostate cancer.[65,66] In addition to their being recognized by bone as "self," the expression of bone-like proteins by prostate cancer cells likely permits them to adhere, proliferate, survive, and participate within the bone microenvironment.[65-68] Successful identification of this protein may permit more accurate prognosis and treatment of metastatic prostate cancer.

Dr. Matthew Smith also presented an update regarding skeletal complications in men with metastatic prostate cancer. The application of bisphosphonates was discussed and is now approved to treat men with bone metastasis from prostate cancer who have failed primary HT.[69,70] Dr. Sartor presented palliation of bone pain with radioisotopes. The trial focusing on strontium-89 was reviewed and appears to offer some benefits as measured by opioid use.[71] Also discussed during this session was the potential of endothelian antagonists and their clinical application. Presented by Dr. Michael Carducci, Phase II data evaluating atrasentan, an endothelin-receptor antagonist, show that it appears to offer a delay in PSA and disease progression as well as reduction of tumor-induced remodeling.[72]

Early trials evaluating pulse calcitriol and docetaxel are promising.

New Systemic Approaches

Application of dendritic cells to instigate an immune response to prostate cancer was presented by Dr. Haakon Ragde. Preliminary results of Phase I/II studies employing a dendritic cell vaccine in hormone-refractory patients appear promising.[73-75] The vaccine appears to be well tolerated, and the majority of the men receiving this vaccine developed a prostate-specific membrane antigen (PSMA)-specific immune response. Preliminary analysis suggests a statistically significant link between clinical outcome and both humeral and cellular immune response to PSMA.[74,75]

Potential advantages of polymeric drug carriers was presented by Dr. Jack Singer. Poly-L-glutamic acid-paclitaxel conjugate was well tolerated and displayed acceptable and enhanced distribution compared to free paclitaxel.[76] Dr. Thomas Beer presented an update of novel therapeutic approaches with taxanes and calcitriol in hormone-refractory disease.[77-78] Early trials evaluating pulse calcitriol and docetaxel are promising. This combination was shown to be well tolerated and displayed measurable disease response rate worthy of continued investigation in Phase III studies.

Issues Concerning Brachytherapy

Dr. Frank Critz presented an overview of current issues regarding brachytherapy. A major concern in the comparison of seed implantation to radical

Main Points

- Screening for free and complexed prostate-specific antigen (PSA) may provide powerful new tools for the study of prostate disease.
- Early clinical trials have shown that taxanes, either as single agents or combined with estramustine, exhibit significant activity in terms of response rate, decline in PSA level, and reduction in bone pain for men with hormone-refractory disease.
- A retrospective study found higher 5-year chemical disease-free survival with 3-dimensional conformal radiotherapy than with standard radiotherapy, with significantly lower toxicity.
- The Selenium and Vitamin E Cancer Prevention Trial (SELECT) is currently recruiting men to assess the effects of selenium and vitamin E, alone and in combination, on the clinical incidence of prostate cancer.
- Defining risk groups using any stratification modality is adequate for predicting PSA outcome for the vast majority of patients with clinically localized prostate cancer; however, it is too soon to tell whether this will succeed in predicting prostate cancer mortality.
- The application of bisphosphonates is now approved to treat men with bone metastasis from prostate cancer who have failed primary hormone therapy.
- Early trials evaluating pulse calcitriol and docetaxel show that this combination is well tolerated and displays measurable disease response rate.
- Urinary obstruction appears to be the major morbidity associated with brachytherapy; preservation of sexual function after brachytherapy appears to compare favorably to radical prostatectomy.

prostatectomy is the issue of disease-free rates. Dr. Critz stressed that due to the prolonged nature of PSA decline in irradiated prostates, minimum follow-up should be at least 27 months, if not 5 years.[79,80] Furthermore, concern regarding the current American Society of Therapeutic Radiation and Oncology definition of biochemical failure in these men may elevate disease-free rates when compared to patients followed using a PSA cut point of above 0.2 ng/mL (ie surgically treated patients).[79–81] Data from a recent study illustrated that when using this end point (PSA > 0.2 ng/mL), men treated with brachytherapy appear to have biochemical disease-free rates comparable to radical prostatectomy.[82,83]

Regarding treatment-related morbidities, Dr. Critz noted that urinary obstruction appears to be the major morbidity associated with brachytherapy. The duration of catheterization for most men is 7 days. Incontinence levels are low following brachytherapy and are related to the incidence of pretreatment transurethral resection of the prostate. Although preservation of sexual function after brachytherapy appears to compare favorably to radical prostatectomy, lack of standardization of comparative analysis remains an issue.[82,83] ■

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